Polycystic ovary syndrome: fertility work-up and treatment strategies

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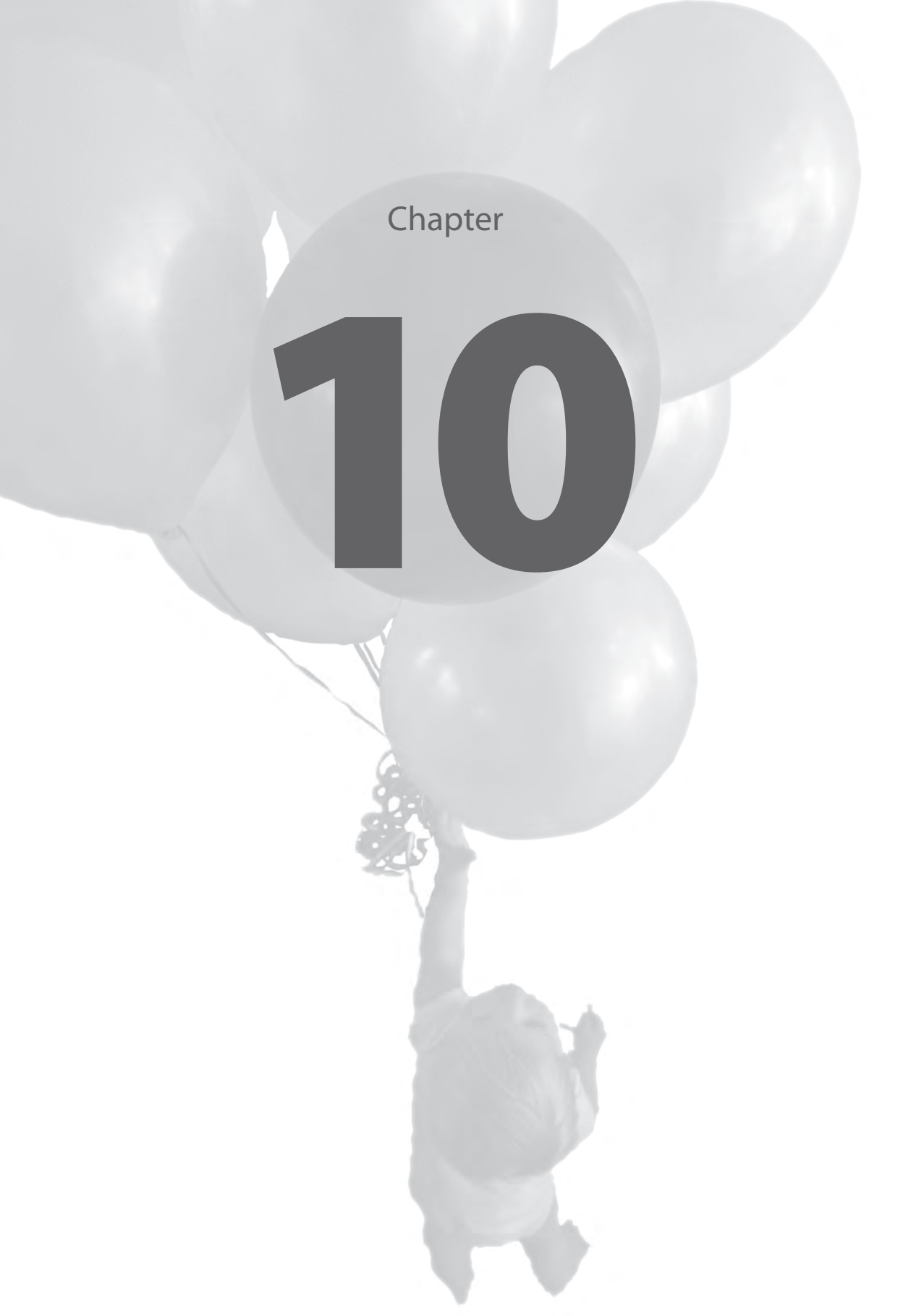

Chapter

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Summary and implications for future research

SUMMARY AND IMPLICATIONS FOR FUTURE RESEARCH

Cycle abnormality is a common reason to seek counselling or treatment, especially for women attempting to become pregnant. Many of these women are subfertile due to chronic anovulation. Polycystic ovary syndrome (PCOS) is the most frequent cause of WHO II anovulation affecting 6 to 10% of women of reproductive age. Although anovulation is such a frequent cause of infertility, evidence on which route to follow regarding diagnosis and treatment is limited and many interventions are based upon tradition and consensus (1,2,3).

Subfertile ovulatory women clearly have to undergo a fertility work-up before eventually starting treatment. It remains to be seen if there is a rationale for such a work-up in anovulatory women. Although the Dutch guidelines, the National Institute for Health and Clinical Excellence guidelines, and the American Society for Reproductive Medicine indicate to explore the risk of other causes of subfertility in specific subgroups, such as male factor, cervical factor or tubal pathology, solid evidence underpinning this, is lacking. Arguments for additional diagnostic testing should be based on the prevalence of an abnormal test in combination with the costs and risk of the test. Without such evidence performing a work-up might lead to unnecessary burden and costs.

When starting ovulation induction, the main goal is to achieve ovulation of preferably one follicle, to obtain a singleton pregnancy. Surgical ovarian wedge resection was the first established treatment for anovulatory PCOS patients, which resulted in regular menstrual cycles and pregnancies(4). This was abandoned because of the high incidence of adhesion formation and introduction of clomiphene citrate and gonadotrophins in the 1960's. Medical ovulation induction as opposed to surgical reduction of the follicle pool has become widespread, which is understandable given the endocrine basis of PCOS and the excellent results obtained. This background probably explains the resistance of many gynaecologists against new surgical approaches aiming to create lesions in the ovaries. These considerations and emotions have probably made widespread implementation of laparoscopic electrocautery of the ovaries impossible, even though electrocautery has been shown to be superior to ovulation induction with gonadotrophins, because it is equally effective and safe, with comparable costs, but with less multiple pregnancies (5,6).

The work presented in this thesis started with the focus on an optimal fertility work-up for women with anovulatory subfertility. What are the consequences of a fertility work-up in these women? Hereafter we studied treatment regimens with the focus on short term effects of ovulation induction with gonadotrophins. What are – if any- the differences between recombinant and urinary gonadotrophins in terms of efficacy, safety, costs and patient acceptability and what is the value of adding metformin to ovulation induction with gonadotrophins. Finally we investigated the long term effects of laparoscopic electrocautery of the ovaries in women who fail to ovulate with clomiphene citrate. Is fear for negative long-term effects of laparoscopic electrocautery justified, or should laparoscopic electrocautery be the treatment of choice for women with clomiphene citrate resistant anovulation?

Chapter one

This chapter describes the clinical entity of PCOS, gives an overview of possible treatment strategies from an historic perspective and gives an outline and description of objectives in this thesis.

Part one: Fertility work-up

Chapter two

The aim of a fertility work-up is to exclude recognized causes of infertility and to distinguish those couples who have good pregnancy prospects from those who have poor prospects. The question thus arises what the optimal fertility work-up in women with PCOS should be since anovulatory subfertile women have a different profile compared to ovulatory subfertile women who have had pregnancy chances for at least one year. To answer this question, we performed a systematic review of the literature to identify data on the prevalence of abnormal diagnostic tests and the association of these test results and the chances to conceive in case ovulation occurs. We distinguished three groups of women: women starting with clomiphene citrate as first-line treatment, women starting with second-line treatment if clomiphene citrate failed to result in pregnancy and women starting second-line treatment if clomiphene citrate failed to result in ovulation, i.e. clomiphene citrate-resistant women. A rational fertility workup in anovulatory women can only be developed if we

know the prevalence of other causes of subfertility, such as male factor, cervical factor or tubal pathology as well as the value of testing for these factors for pregnancy chances in these women at different stages of treatment.

In our search we found four studies reporting on 3,017 women starting with clomiphene citrate as first-line treatment. The prevalence of male factor subfertility was 10% and in 0.3 % of couples azoospermia was found (two studies). The prevalence of bilateral tubal disease was 4% (two studies). Male factor subfertility (total motile count post processing above 1 million) was not associated with pregnancy chances in couples with PCOS (one study).

Three studies reported on 462 women starting with second-line treatment if clomiphene citrate resulted in ovulation but failed to result in pregnancy. Semen parameters were not predictive for pregnancy (one study). The prevalence of bilateral tubal disease in these women was 8% (three studies).

Two studies reported on 168 clomiphene citrate-resistant women and total motile sperm count did not predict live birth. For all other outcomes no studies were available.

Based upon the scarce evidence collected in this review it is impossible to make firm recommendations for the performance and timing of the basic fertility work-up in anovulatory women. It is our personal view that the basic fertility work-up in women starting with clomiphene citrate as first- line treatment should be limited to a semen analysis. Compared to subfertile ovulatory women, 25 times as many semen analyses should be performed to detect one abnormal sperm test. Still, as a semen analysis is an inexpensive test without any risk, doing this test remains beneficial. This does not apply to tubal patency testing. As only 4% of women have bilateral tubal obstruction, and tubal patency tests are expensive and have a higher risk of complications as compared to a semen analysis, tubal patency testing should not be carried out in these women.

Our advice is to start ovulation induction with clomiphene citrate for every woman with PCOS, except for those with azoospermia. In women who need to start second-line treatment if clomiphene citrate failed to result in pregnancy or ovulation we suggest to perform a tubal patency test. We found that bilateral tubal disease was observed in 4% of women starting with first-line treatment, while 8-9% of women starting second line treatment had evidence for bilateral tubal obstruction. This is comparable to women with other causes of subfertility, which may validate assessment of patency of the tubes. Earlier

testing means more frequent unnecessary testing, carrying additional risks and generating costs. In women with clomiphene citrate-resistance laparoscopic electrocautery is superior over ovulation induction with gonadotrophins and tubal assessment can easily be performed during the same procedure.

Chapter three

The question whether a postcoital test should be performed could not be answered in the previous chapter. Chapter three describes the result of a prospective follow-up study which was performed to examine the capacity of the postcoital test to predict pregnancy in WHO II anovulatory women who become ovulatory on clomiphene citrate. In this study, 251 women were included and a postcoital test was planned in one of the first three ovulatory cycles. Regardless of the postcoital test result, women continued ovulation induction with clomiphene citrate for at least six ovulatory cycles. The primary outcome was time to ongoing pregnancy. In 152 women the postcoital test was performed; 41 women were pregnant before the postcoital test, 10 had persistent anovulation, and for various reasons the postcoital test was not performed in the remaining 48 women. Among the 152 women, 107 had a positive postcoital test and 45 women had a negative postcoital test result. For 17 women with a negative test this could not be repeated as indicated. In most cases because women were pregnant (n=6), switched (n=2) or discontinued (n=4) treatment. The ongoing pregnancy rate was 45/107 (42%) for women with a positive test and 10/28 (36%) for women with a negative postcoital test. The proportional hazard analysis showed that the postcoital test results had no influence on time to ongoing pregnancy, with a HR of 1.3 (95% CI 0.64 – 2.5). When ranking women, with a well-timed PCT, based on clarity of the mucus, women with clear mucus had a significantly higher change of an ongoing pregnancy. Thirty five of 77 (46%) women with clear mucus had an ongoing pregnancy versus 12 of 45 (27%) women in whom the mucus was not clear (HR 2.0; 95% CI 1.02-3.84, p=0.04). Compared to all other groups, the subgroup of women with a negative PCT and cervical mucus of poor quality had the lowest chance on an ongoing pregnancy (22%). This could in theory be the group that benefits from doing a PCT and a mucus determination. However, this group accounted for only 7 % of the 250 women included in this study and therefore probably not worth of doing, especially since the PCT may result in emotional stress. In summary, the findings of this prospective cohort study

demonstrated that the postcoital test has only limited value in women with WHO II anovulation, ovulatory with CC. We advocate that women who start ovulation induction with CC can safely do so without performing a PCT.

Part two: Ovulation induction with gonadotrophins

Chapter four

Once ovulation induction with gonadotrophins is started in case women fail to ovulate or fail to get pregnant with clomiphene citrate, urinary and recombinant preparations are available and a decision must be made which one to use. Differences between recombinant and urinary gonadotrophins in the efficacy, safety, costs and patient acceptability are of importance. The latest review comparing these two medication dates from 2001. We searched for more recent data in the Cochrane, Medline and Embase databases up to November 2008. An additional three randomised controlled trials were found. A total of six randomised controlled trials were included in this review comparing recombinant and urinary gonadotrophins for ovulation induction. Four trials compared follitropin alpha with highly purified urofollitropin, one trial compared follitropin alpha with highly purified human menopausal gonadotrophins and one trial compared follitropin beta with highly purified urofollitropin. A total of 862 women were included. Pooling these data resulted in a significantly higher ovulation rate after recombinant gonadotrophins in comparison to urinary gonadotrophins (OR 1.40; 95% CI 1.03–1.92). This did not lead to higher pregnancy rates. No significant differences were observed for live birth rate (OR 1.12; 95% CI 0.75–1.66), ongoing pregnancy rate (OR 1.27; 95% CI 0.78–2.07), clinical pregnancy rate (1.13; 95% CI 0.67–1.89) or multiple pregnancy rate (OR 0.68; 95% CI 0.34–1.36). Only one case of severe ovarian hyperstimulation syndrome was reported for all women included. The costs per cycle were compared in two trials and in both the cost per cycle was higher for recombinant gonadotrophins as compared to urinary gonadotrophins even though in both trials a lower recombinant dose could be used, with a shorter duration of stimulation. Both preparations were acceptable for women and the patient acceptability was mainly influenced by the mode of administration. Summarizing these data we conclude that there is no difference in effectiveness, safety and acceptability between recombinant and urinary gonadotrophins.

Recombinant gonadotrophins may be more convenient to use due to the ease of self-administration, but they are also more expensive than the urinary products.

Chapter five

Insulin resistance is a common feature of PCOS. The association between insulin resistance and anovulation has led to a novel and promising therapy of administering insulin-sensitising drugs to women with PCOS in an effort to restore ovulation and enhance pregnancy. Of the insulin-sensitising drugs, metformin has been the one studied most widely and has the most reassuring safety profile.

We evaluated the use of metformin added to gonadotrophins for ovulation induction. This review relied on the search strategy developed for the Cochrane Menstrual Disorders and Subfertility Group and described in the Cochrane database. In this Cochrane review we selected studies that compared metformin with placebo during ovulation induction with gonadotrophins in women with PCOS, starting second line treatment if clomiphene citrate failed to result in ovulation or pregnancy. Four studies were included in this review, with a total of 154 women. None of the trials demonstrated a significant difference in the primary outcome live birth rate or ongoing pregnancy rate (OR 2.18, 95% CI 0.93 - 5.08). Clinical pregnancy rate was significantly higher for women treated with metformin (OR 2.35, 95% CI 1.12 - 4.93). There was no evidence for a difference in ovarian hyperstimulation syndrome rate (one trial; OR 0.32; 95% CI 0.01 to 8.23). However, as the power to show a difference was too low due to number and size of the individual trials, and as the clinical pregnancy rate was significantly in favour of the use of metformin, we suggest that metformin can be used in all women starting ovulation induction with gonadotrophins, with the caveat that more trials on the subject are needed.

Chapter six

Guidelines on treatment strategies for ovulation induction in women with anovulation currently do not provide evidence based advice on when treatment in women ovulatory with clomiphene citrate should be switched to ovulation induction with gonadotrophins and / or intrauterine insemination. The NICE guidelines recommend (without evidence) intrauterine insemination and prolonged ovulation induction with clomiphene citrate in women that

ovulate on clomiphene citrate but do not conceive. This chapter presents the protocol for a multicentre randomised controlled trial within the Netherlands in which the most optimal treatment strategy for women with clomiphene citrate failure will be explored (M-OVIN study). Pregnancy rates with gonadotrophins can expected to be higher than with clomiphene citrate in women that do not conceive after six ovulatory cycles on clomiphene citrate. The downside is that ovulation induction with gonadotrophins implies daily injections of gonadotrophins combined with concurrent blood and ultrasound monitoring of follicular growth and development. There is a risk of multifollicular development, despite careful dose adjustment and monitoring, due to the inherent nature of PCOS. Also, injectable gonadotrophins are expensive and the frequent monitoring of follicular growth adds substantially to this. Extra costs are generated because treatment cycles often have to be cancelled to minimize the risks of multiple pregnancy and, more rarely, of ovarian hyperstimulation syndrome. In intrauterine insemination motile spermatozoa are concentrated and placed directly into the uterine cavity, in closer proximity to the released oocyte than is the case after vaginal intercourse. There have been no trials that studied the effect of intrauterine insemination in women undergoing ovulation-induction with clomiphene citrate or gonadotrophins for oligo- or anovulation. Still, intrauterine insemination is often added to ovulation induction with clomiphene citrate or gonadotrophins. Intrauterine insemination is expected to result in higher pregnancy rates than intercourse but requires extra laboratory work and more hospital visits and is therefore more expensive.

The objective of this study is to assess the cost-effectiveness of extended treatment with clomiphene citrate compared to treatment with gonadotrophins and / or the use of intrauterine insemination, in women who had six ovulatory cycles after clomiphene citrate, but did not conceive. Primary outcome will be birth of a healthy child. Secondary outcomes are clinical pregnancy, ongoing pregnancy, miscarriage, multiple pregnancy, patients' preference and costs. Two comparisons will be made, one in which clomiphene citrate is compared to gonadotrophins and one in which the addition of intrauterine insemination is compared to intercourse.

Part 3: Long-term outcomes after laparoscopic electrocautery of the ovaries

Chapter seven

Laparoscopic electrocautery of the ovaries is an alternative to ovulation induction with gonadotrophins in women with clomiphene citrate-resistant PCOS and frequently leads to ovulation, but adhesion formation has been described for up to 70 percent. In view of this, there are ongoing concerns about long-term effects of electrocautery, for example secondary infertility due to tubal obstruction or premature ovarian failure. Data from proper cohorts comparing these two methods on pregnancy rate, including ectopic pregnancy rate and menstrual cycle regularity are lacking. We performed a long-term follow-up study of a randomised controlled trial comparing laparoscopic electrocautery of the ovaries and ovulation induction with gonadotrophins in women with clomiphene citrate-resistant PCOS. In this trial 168 clomiphene citrate-resistant women with PCOS were included between 1998 and 2001. All women had anovulation and polycystic ovaries on ultrasound. These women were allocated to electrocautery strategy entailing laparoscopic electrocautery of the ovaries followed by ovulation induction with clomiphene citrate or gonadotrophins when anovulation persisted compared to ovulation induction with gonadotrophins. The ovaries of women allocated to electrocautery were cauterized with an Erbotom ICC 350 Unit (Erbe; Zaltbommel, Netherlands), bipolar insulated needle electrode and each ovary was punctured randomly 5-10 times, depending on its size. The automatic stop function guaranteed a reproducible coagulation time. If women ovulated in six subsequent cycles no further treatment was given. If anovulation persisted for eight weeks, treatment was followed by clomiphene citrate. Treatment was followed by recombinant gonadotrophins if anovulation persisted with clomiphene citrate 150 mg per day for five days. Women allocated to the recombinant gonadotrophins strategy were treated with recombinant gonadotrophins starting on day three of the cycle according to the low-dose step-up regime.

After eight to twelve years of follow-up we were able to obtain follow-up data for 159 of the 168 women (95%): 79 of 83 women allocated to the electrocautery strategy (95%) and 80 of 85 women allocated to ovulation induction with gonadotrophins (94%). The cumulative proportion of women with a first child was 86% (71 of 83 couples) for women who had been allocated

to electrocautery versus 81% (69 of 85 couples) for women who had been allocated to ovulation induction with gonadotrophins (RR 1.1; 95% CI: 0.92 to 1.2). Treatment with electrocautery resulted in a significantly lower need for stimulated cycles to reach a live birth; 53% after electrocautery versus 76% after ovulation induction with gonadotrophins (RR 0.69; 95% CI 0.55 to 0.88). The cumulative proportion of women with a second child was 61% after electrocautery versus 46% after ovulation induction with gonadotrophins (RR 1.4; 95% CI: 1.00 to 1.9). Overall, there were 7 twins out of 134 deliveries (5%) after electrocautery versus 10 twins out of 124 deliveries (8%) in women allocated to gonadotrophins (RR 0.65; 95% CI: 0.25 to 1.6). Miscarriage rate and ectopic pregnancies were comparable. Thus, after 8–12 years of follow-up the cumulative chances of delivering at least one live born baby were not lower for women allocated to the electrocautery strategy group compared to women allocated to the gonadotrophin strategy, but 5% higher, though not significantly different. We also observed that electrocautery significantly increased the number of women with a second child. Electrocautery eliminated the need for ovulation induction or ART for the first child. The high intrauterine pregnancy rate and low ectopic pregnancy rate clearly demonstrate that post-operative adhesion formation, if at all present, is not an important clinical problem. None of the women in our study had peri-operative complications.

Chapter eight

Costs do play an important role in deciding which treatment to give to a woman. As available data only concerns short-term outcome, we assessed the long-term costs of laparoscopic electrocautery of the ovaries compared to ovulation induction with gonadotrophins in women with clomiphene-resistant PCOS.

Given the equivalence between the two treatment strategies in terms of a first live birth, our economic analysis focused on the cost difference between the two strategies within a mean follow-up time of eight to twelve years. The mean costs per first live birth after randomisation were €11,176 (95% CI €9,689 to €12,549) for the electrocautery group and €14,423 (95% CI €12,239 to €16,606) for women allocated to ovulation induction with gonadotrophins, resulting in significantly lower costs per first live birth for women allocated to the electrocautery group (mean difference €3,220; 95% CI €650 to €5,790). We observed that electrocautery significantly eliminated the need for ovulation induction or ART for the first child. If ovulation induction was needed,

significantly more clomiphene citrate, but significantly less rFSH was needed. With this long-term follow-up study we have shown that both laparoscopic electrocautery of the ovaries and ovulation induction with gonadotrophins are safe and effective treatments in women with clomiphene citrate resistant PCOS. Laparoscopic electrocautery of the ovaries results in significantly lower costs per live birth than ovulation induction with gonadotrophins.

Chapter nine

Women with PCOS have a higher risk for development of gestational diabetes or hypertensive disorders during pregnancy and metabolic or cardiovascular disease at long-term. Insulin resistance and genetic predisposition for metabolic syndrome play an important role. In the same women described in chapter seven we additionally evaluated whether laparoscopic electrocautery has an effect on occurrence of gestational diabetes, hypertensive disorders during pregnancy or metabolic or cardiovascular disease. The mean female age at follow-up was 40 years and the average BMI was 27.5. In total, 13 of 68 women (19%) allocated to electrocautery strategy and for 14 of 63 women (22%) allocated to ovulation induction with gonadotrophins had evidence for gestational diabetes or hypertensive disorders during pregnancy (RR 0.86; 95% CI 0.43 to 1.7). At the moment of contact, 12 of 69 (17%) women allocated to electrocautery strategy and 13 of 69 (19%) women allocated to ovulation induction with gonadotrophins had evidence for diabetes, hypertension, cardiovascular disease (RR 0.90; 95% CI 0.39 - 2.1). The risk of these metabolic or cardiovascular disease was modified by BMI, but not by female age or treatment. Fifty-four per cent of the women allocated to electrocautery had a regular menstrual cycle 8–12 years after randomisation versus 36% in those allocated to ovulation induction with gonadotrophins (RR: 1.5; 95% CI: 0.87–2.6). No women had her last menstruation more than one year ago. We conclude that laparoscopic electrocautery of the ovaries in women with clomiphene citrate resistant PCOS does not affect pregnancy complications or metabolic or cardiovascular disease later in life compared to medical ovulation induction with gonadotrophins.

Recommendations and implications for future research

The findings in this thesis demonstrate that there is no rationale for a complete fertility work-up in women with PCOS except for a semen analysis when women start ovulation induction with clomiphene citrate. A postcoital test in women ovulatory with clomiphene citrate only leads to additional burden and costs, without an increase in pregnancy rate and should therefore not be performed. Tubal patency testing should be performed when first-line treatment fails. Once there is an indication for ovulation induction with gonadotrophins, because women fail to get pregnant with clomiphene citrate or fail to ovulate or get pregnant after laparoscopic electrocautery in women with clomiphene citrate-resistant PCOS, urinary and recombinant gonadotrophins are equally effective for ovulation induction. Thus the gonadotrophin with the lowest costs and highest patient acceptability is the gonadotrophin of choice. We suggest that metformin can be added to ovulation induction with gonadotrophins, as this lead to a higher clinical pregnancy rate and non-significant induction of ongoing pregnancy rate, under the statement that more trials are needed. Laparoscopic electrocautery should be the treatment of first choice for women with clomiphene citrate-resistant PCOS as this leads to more live born children with lower costs per live born child as compared to ovulation induction with gonadotrophins.

The addition of metformin to gonadotrophins for ovulation induction leads to a significantly higher clinical pregnancy rate. The chance for an ongoing pregnancy rate / live birth rate was two times higher with the addition of metformin, but this did not lead to a significant difference. Only four studies were included in this review, with a total of 154 women. A beneficial effect of metformin on live birth rate is very likely and with an additional trial added to this meta-analysis enough power would be reached to assess a statistical significant difference.

Laparoscopic electrocautery is the dominant strategy in women with clomiphene citrate-resistant anovulation in terms of live birth rates and costs. Electrocautery in women with clomiphene citrate-resistant PCOS does not affect pregnancy complications or metabolic or cardiovascular disease later in life compared to ovulation induction with gonadotrophins. However, these

data are solely based on postal questionnaires. Value would be added to these data when blood pressure, glucose levels and ovarian reserve by ultrasound and / or FSH / AMH value are measured in these women.

We do not know when to switch to ovulation induction with gonadotrophins when women ovulate with clomiphene citrate but do not get pregnant. The guidelines now indicate to continue for six to twelve cycles. The data to provide the answer which treatment should be continued after six ovulatory cycles with clomiphene citrate will become available once the M-OVIN study has been completed.

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